Author's response to reviews

Title: Quality of life and metabolic status in mildly depressed patients with type 2 diabetes treated with paroxetine: A double-blind randomised placebo controlled 6-month trial

Authors:
Maria Paile-Hyvarinen (maria.paile@helsinki.fi)
Kristian Wahlbeck (kristian.wahlbeck@stakes.fi)
Johan G Eriksson (johan.eksson@helsinki.fi)

Version: 4 Date: 15 February 2007

Author's response to reviews: see over
Dear Editor,

We are grateful for the excellent comments and suggestions by all of the reviewers. In this letter we will list the changes made to the manuscript and address the reviewers’ comments point by point:

General comments:

1. We have reanalysed our data using ANCOVA as the reviewers suggested and included analysis of the data at three months.

2. Because of the new methods and results we have rewritten the tables and figures in the manuscript. We have also excluded some of the irrelevant information from the previous version of the manuscript.

3. We have no longer used last observation carried forward analysis because all but one off the dropouts occurred before we had obtained any data to carry forward.

4. One subject who was previously included in the analyses was now regarded as a dropout before initiation of the study. The previous mistake occurred because this subject had actually received his medication but in effect never started taking it and never returned for further analysis. The number of subjects is corrected both in text and tables.

5. We have corrected misspellings and incoherencies as advised.

6. We have decided to call the quality of life questionnaire SF-36 instead of RAND-36 since this name is more commonly used in the literature.

Reviewer: Ruth S Weinstock

1. Regarding sufficient sample size we refer to the comment by the statistics referee, Mr John M Hughes.

2. We have now explained in more detail why subjects dropped out. Unfortunately we were not able to recruit more subjects though it would undoubtedly have added power to our results.

3. The study was not powered to detect a difference in RAND-36 (now SF-36). We have modified the manuscript to add clarity in this aspect.

4. We have modified the tables and tried to avoid incoherencies between text and tables.

Reviewer: Miranda van Tilburg
Major Compulsory Revisions:
1. Our decision to exclude moderately to severely depressed patients was based on the conviction that a six month period of placebo treatment is unethical in these circumstances. In line with this we did not have ethical permission for this type of study design. When a potential trial participant was found to be depressed we organised immediate psychiatric counselling free of charge. A shorter trial would have been another way to go about it, but we were particularly interested in the long term effects of paroxetine on glucose metabolism.

2. We do not consider it unethical to have treated non-depressed subjects with paroxetine since the adverse effects of paroxetine are known to be mild and our hypothesis was that the diabetic subjects would benefit from the treatment in terms of improved glucose tolerance regardless of their mental status. Many of the previous trials with SSRI for diabetics have been performed on mentally healthy subjects.

3. We have performed analysis of covariance as suggested.

Minor Essential Revisions:
1. We have modified the methods section to be more clear regarding the psychiatric interview.

2. We have stated more clearly which number of subjects was used in the analysis.

3. The subgroup analysis was moved to the results section. We are of course aware of the problems with the small numbers and therefore we do not attempt on drawing any conclusions from this result.

4. We have no longer used last observation carried forward analysis.

5. We have clarified the time point of analysis in text and tables.

Discretionary revisions:
1. Unfortunately we have taken only safety blood tests after one month and have no meaningful data to analyse at that time point.

2. Our lack of clarity regarding the effects of SSRI on metabolic control is due to the fact that there is no simple explanation to it. There is evidence to suggest both a metabolic and a psychological pathway.

Reviewer John M Hughes:
1. We have used ANCOVA instead of Mann-Whitney as advised.

2. The clinically important difference in GHbA1c has been stated in the text whereas there is no consensus as to what is a clinically important change in RAND-36 (SF-36).
We originally calculated power assuming a standard deviation of 0.9%-units in GHbA1c. At the end of the trial there was only 37 subjects left. The actual standard deviation of the sample GHbA1c was 1.1 and the achieved power to detect a 0.8%-units difference was 59%. Achieved power to detect a 10p difference in SF-36 was 45%.

Points 3-5 have been addressed above.

6. Adverse events have been tabulated as suggested.

7. Information on ethical approval is given in the methods section.